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Abstract

We studied the association of fatty liver with subcutaneous and visceral obesity in 46 male and 36 female patients with body mass index (BMI) over 22 kg/m2. The correlation coefficient between the ratio of the visceral adipose tissue to the subcutaneous adipose tissue (V/S) and the computed tomography (CT) number of the liver was -0.299 ($P < 0.05$) and that between the V/S ratio and the ratio of the CT number of the liver to that of the spleen (CT-L/CT-S) was -0.335 ($P < 0.05$) in the males. Partial correlation analysis after making correction for BMI showed an increased correlation coefficient of -0.485 ($P < 0.05$) between the V/S ratio and the CT-L/CT-S ratio in the males. The odds ratio in the males for CT-L/CT-S below 1.0 and V/S above 1.0 was 3.25 with a 95% confidence interval of 1.02 to 9.39. No such association between the V/S ratio and the CT-L/CT-S ratio was present in the female patients. Multiple regression analysis with serum level of alanine aminotransferase, a marker of fatty liver, as an independent variable revealed a partial regression coefficient of -17.7 for CT-L/CT-S ($P < 0.05$) in the males and -21.7 ($P < 0.05$) in the females, validating the CT-L/CT-S ratio as an index of fatty liver. The results indicate the association of fatty liver as determined by the CT-L/CT-S ratio with visceral obesity in males.

KEYWORDS: fatty liver, visceral obesity, computed tomography number

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Association of Fatty Liver with Increased Ratio of Visceral to Subcutaneous Adipose Tissue in Obese Men

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We studied the association of fatty liver with subcutaneous and visceral obesity in 46 male and 36 female patients with body mass index (BMI) over 22 kg/m^2. The correlation coefficient between the ratio of the visceral adipose tissue to the subcutaneous adipose tissue (V/S) and the computed tomography (CT) number of the liver was -0.299 ($P < 0.05$) and that between the V/S ratio and the ratio of the CT number of the liver to that of the spleen (CT-L/CT-S) was -0.335 ($P < 0.05$) in the males. Partial correlation analysis after making correction for BMI showed an increased correlation coefficient of -0.485 ($P < 0.05$) between the V/S ratio and the CT-L/CT-S ratio in the males. The odds ratio in the males for CT-L/CT-S below 1.0 and V/S above 1.0 was 3.25 with a 95% confidence interval of 1.02 to 9.39. No such association between the V/S ratio and the CT-L/CT-S ratio was present in the female patients. Multiple regression analysis with serum level of alanine aminotransferase, a marker of fatty liver, as an independent variable revealed a partial regression coefficient of -17.7 for CT-L/CT-S ($P < 0.05$) in the males and -21.7 ($P < 0.05$) in the females, validating the CT-L/CT-S ratio as an index of fatty liver. The results indicate the association of fatty liver as determined by the CT-L/CT-S ratio with visceral obesity in males.

Key words: fatty liver, visceral obesity, computed tomography number

Fatty liver is a common pathological state of the liver associated with obesity and other disorders of lipid and carbohydrate metabolism. It is frequently detected by slight elevations of alanine aminotransferase (ALT) (1) and γ-glutamyltransferase (GGT) (2) levels in serum. Obesity has been divided recently into two distinct types by Tarui and his group: visceral obesity and subcutaneous obesity (3). The importance of increased visceral fat as a factor in accelerating atherosclerosis has been shown by them. On the other hand, fatty liver is not significant as a liver disease requiring medical treatment other than as a condition for prevention of life style-related diseases: ishchemic heart diseases, cerebral infarction or diabetes mellitus. The ratio of the area of the visceral adipose tissue (V) to the area of subcutaneous adipose tissue (S) is expressed in V/S. It is therefore interesting to know whether the fatty liver is associated with the increased V/S ratio.

This study was carried out in an attempt to see whether there is any correlation between the extent of fat deposition in the liver and the V/S ratio. The usefulness of using the ratio of the computed tomography (CT) number of the liver (CT-L) to the CT number of the spleen (CT-S) as an index of fatty liver was also studied in terms of eliminating possible common conditions that alter the CT numbers of these two organs.

Subjects and Methods

Subjects. A total of 83 Japanese patients, 47 males and 36 females, ranging in age from 22 to 76 years old for men and 26 to 83 for women, were randomly

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selected from the out-patient clinics of three hospitals in Okayama District, Kawasaki Medical School Hospital, Yura Hospital and Shigei Medical Research Hospital, on the basis of the following criteria: a) patients without major hepatic diseases, such as hepatitis, cirrhosis or primary and secondary liver cancers; b) patients without other neoplastic or terminal diseases; and c) patients whose body mass index (BMI) was equal to or greater than 22. All the patients were conscious, were able to narrate by themselves their history of alcohol intake, and gave consent for CT examination and blood analysis.

Methods. The ratio of CT-L/CT-S was used as a measure of the extent of fatty liver based on a high inverse correlation existing between CT-L and fatty change of the liver as observed histologically (4). This correlation was also observed on CT films during routine procedure for the diagnosis of fatty liver from a low CT-L relative to that of the spleen (5, 6). The value of BMI was arbitarily set as equal to or greater than 22, which is a mean suggested ideal value of BMI (7). CT scanners (HI Light Advantage, GE, USA, W 400-20 Hitachi, Tokyo, Japan and Somatom SRSP, Seimens, Germany) with a built-in digitizer were used with comparable results. Patients in the supine position were scanned at the umbilical level and a level giving maximum images of the liver and the spleen (8). To visualize adipose tissue and make them distinguishable from the surrounding tissues, a window value of 500 and a center around -50 HU were used according to Tokunaga *et al.* (8). By means of the window setting, the CT scanned at the umbilical level revealed a clearly defined subcutaneous fat layer between the skin and the muscle with a CT number range of -50 to -140 HU as well as visceral adipose tissue in the intraperitoneal part that had the same density as the subcutaneous fat layer (8). CT-L and CT-S were obtained by setting 5-10 regions of interest (ROI's) in both organs and taking average CT numbers after checking that no difference exsisted among the ROI's. This allowed us to study diffuse fatty change. The ratio of CT-L/CT-S < 1 and the ratio of V/S $\geqq 1$ considered to be convenient indices of fatty liver and visceral obesity, respectively, were used to calculate the odds ratio between them.

In order to analyze conditions related to the decreased ratio of CT-L/CT-S, the markers of hepatic dysfunction, serum ALT, aspartate aminotransferase (AST) and GTT, and other biochemical tests related to lipid metabolism, such as serum triglycerides, cholesterol and high-density lipoprotein (HDL) cholesterol and non-esterified fatty acids (NEFA), were included in this study. Correlation analyses were made to find the association between the CT-L/CT-S ratio, the V/S ratios and the biochemical results and to eliminate possible confounding factors among them. Multiple regression analysis with respect to ALT was also employed to validate the CT-L/CT-S ratio as an index of fatty liver.

Results were expressed in means $\pm$ standard deviations for comparison and evaluation of differences between male and female patients by the Student's t test. Correlation analysis, partial correlation analysis and multiple regression analysis were performed using the statistical package PC SAS, Version 1.01.

Results

Age, obesity and fatty liver-related indices and the results of blood biochemistries obtained for male and female patients are compared in Table 1. In the studied population, the males had a significantly lower cholesterol level and BMI than the females, while the V/S ratio was significantly higher in the males than in the females. No

Table 1 Age, blood biochemistries and indices of fat deposition in male and female patients

	Male Number of cases		Female Number of cases	
Age (years)	47	51.6 ± 13.9	35	57.1 ± 14.7
BMI (kg/m^2)	47	26.0 ± 2.9	36	27.5 ± 2.8
V/S	47	1.05 ± 0.51	36	0.72 ± 0.41
CT-L	47	51.3 ± 11.6	36	50.0 ± 13.6
CT-S	47	47.9 ± 6.9	36	45.4 ± 8.0
CT-L/CT-S	47	1.07 ± 0.22	36	1.14 ± 0.36
ALT (IU/l)	39	26.8 ± 16.0	31	27.4 ± 20.7
AST (IU/l)	39	20.1 ± 8.7	31	21.7 ± 10.4
GGT (IU/l)	40	33.0 ± 23.1	24	25.0 ± 18.2
Triglycerides (mg/dl)	44	136 ± 86	30	158 ± 71
Cholesterol (mg/dl)	44	198 ± 37	29	218 ± 33
HDL-cholesterol (mg/dl)	38	44.9 ± 15.6	28	51.6 ± 13.9
NEFA (mEq/l)	32	0.62 ± 0.24	26	0.67 ± 0.40

*, $P < 0.05$; **, $P < 0.01$.

BMI: Body mass index; V/S: Ratio of visceral adipose tissue to the subcutaneous adipose tissue; CT-L: Computed tomography (CT) number of the liver; CT-S: CT number of the spleen; ALT: Alinine amino transferase; AST: Aspartate amino transferase; GGT: Gamma glutamyl transferase; HDL: High-density lipoprotein; NEFA: Non-esterified fatty acid.

other variables showed significant differences. Based on these results the male and female groups were analyzed separately.

The results of correlation analysis on the data of 35 males available for all the varibles in Table 1 are given in Table 2. A significant positive correlation existed between CT-L and CT-S, suggesting the presence of common factors contributing to the CT densities of both the liver and the spleen. The CT-L/CT-S ratio which represents fatty change of the liver corrected for the common factors showed a significant negative correlation with the V/S ratio ($r = -0.395$, $P < 0.05$), indicating that the fatty change of the liver had a positive correlation with the visceral obesity. However, the V/S ratio failed to show significant correlation with CT-L, ALT as another marker of fatty liver, BMI or other variables of blood lipids which are generally considered to be related to visceral obesity. Incidentally, ALT showed significant correlation with age, AST, GGT, cholesterol and HDL-cholesterol, while AST correlated with BMI and triglycerides but not with age.

When correlation coefficients were calculated with the variables available for all the 47 males given in Table 1, a similar significant negative correlation (Table 3) was found between CT-L/CT-S and V/S ($r = -0.335$, $P < 0.05$) and also between V/S and CT-L ($r = -0.300$, $P < 0.05$) in addition to the significant positive correlation existing between CT-L and CT-S ($r = 0.490$, $P < 0.001$). The actual values of CT-L and the ratio of CT-L/CT-S are plotted against the V/S ratio in Figs. 1 and 2, respectively, for the males.

The data for men given in Table 2 were further analyzed to calculate partial correlation coefficients by correcting for a possible confounding factor related to BMI, and the results are given in Table 4. In this analysis the correlation coefficients existing between the CT-L/CT-S ratio and the V/S ratio showed a larger negative value ($r = -0.485$, $P < 0.05$), thus consolidat-

Table 2 Correlation matrix of the listed variables based on 35 males who had available data for all the corresponding variables

	Age	BMI	V/S	CT-L	CT-S	CT-L/CT-S	ALT	AST	GGT	TG	Chol.	HDL-Chol.
Age	1.000											
BMI	0.076	1.000										
V/S	0.165	−0.108	1.000									
CT-L	0.155	0.168	−0.327	1.000								
CT-S	−0.127	0.097	0.127	0.407*	1.000							
CT-L/CT-S	0.237	0.089	−0.395*	0.633**	−0.433**	1.000						
ALT	−0.510**	0.329	0.076	−0.186	0.205	−0.314	1.000					
AST	−0.232	0.410*	−0.069	−0.038	0.223	−0.192	0.661**	1.000				
GGT	−0.327	0.118	0.079	−0.131	0.082	−0.174	0.688**	0.689**	1.000			
Triglycerides	−0.181	−0.003	−0.097	−0.143	−0.006	−0.161	0.048	0.242	0.478**	1.000		
Cholesterol	−0.208	0.412*	−0.119	0.250	0.321	−0.010	0.368*	0.464**	0.481**	0.442**	1.000	
HDL-cholesterol	−0.269	0.222	−0.137	0.069	0.184	−0.051	0.353*	0.401*	0.227	−0.158	0.264	1.000

*; **; BMI; V/S; CT-L; CT-S; ALT; AST; GGT; HDL: See legend to Table 1. TG: Triglycerides; Chol.: Cholesterol.

Table 3 Correlation coefficients among age and indices of fat deposition in 47 males

	Age	BMI	V/S	CT-L	CT-S
Age	1.000				
BMI	0.003	1.000			
V/S	0.244	0.035	1.000		
CT-L	0.238	−0.057	−0.299*	1.000	
CT-S	−0.057	−0.033	0.042	0.491**	1.000
CT-L/CT-S	0.287	−0.055	−0.335*	0.755**	−0.182

*; **; BMI; V/S; CT-L; CT-S: See legend to Table 1.

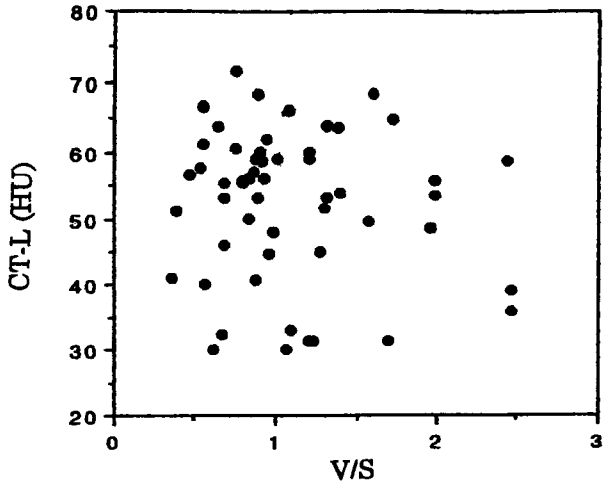

Fig. 1 Comparison of CT-L with V/S ratio in the males. CT-L: Computed tomography number of the liver; V/S: Visceral adipose tissue to the subcutaneous adipose tissue.

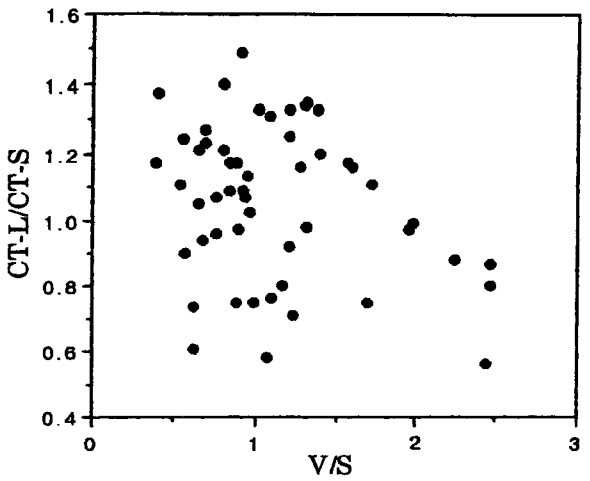

Fig. 2 Comparison of CT-L/CT-S ratio with the V/S ratio in the males. CT-S: Computed tomography number of the spleen. CT-L; V/S: See legend to Fig. 1.

Table 4 Partial correlation matrix of the listed variables based on the data of 35 males given in Table 2

	Age	V/S	CT-L	CT-S	CT-L/CT-S	ALT	AST	GGT	TG	Chol.	HDL-Chol.
Age	1.000										
V/S	0.228	1.000									
CT-L	0.112	−0.430*	1.000								
CT-S	−0.191	0.187	0.336	1.000							
CT-L/CT-S	0.228	−0.485*	0.641**	−0.489*	1.000						
ALT	−0.414*	0.346	−0.087	0.351	−0.324	1.000					
AST	−0.180	0.252	−0.087	0.329	−0.307	0.672**	1.000				
GGT	−0.239	0.158	−0.042	0.124	−0.128	0.669**	0.795**	1.000			
Triglycerides	−0.238	−0.158	−0.064	−0.007	−0.083	−0.006	0.349	0.569**	1.000		
Cholesterol	−0.353	0.036	0.208	0.340	−0.057	0.458*	0.474*	0.664**	0.551**	1.000	
HDL-cholesterol	−0.338	0.047	0.138	0.330	−0.082	0.390	0.237	0.089	−0.335	−0.048	1.000

*; **; V/S; CT-L; CT-S; ALT; AST; GGT; HDL: See legend to Table 1. TG; Chol.: See legend to Table 2.

Table 5 Correlation matrix of the listed variables based on 25 females who had available data for all the corresponding variables

	Age	BMI	V/S	CT-L	CT-S	CT-L/CT-S	ALT	AST	GGT	TG	Chol.
Age	1.000										
BMI	−0.110	1.000									
V/S	0.106	−0.056	1.000								
CT-L	0.404	0.125	−0.080	1.000							
CT-S	0.105	0.267	0.128	0.152	1.000						
CT-L/CT-S	0.239	0.001	−0.163	0.734**	−0.483*	1.000					
ALT	−0.737**	0.206	−0.063	−0.633**	0.170	−0.568**	1.000				
AST	−0.676**	0.323	−0.104	−0.207	0.323	−0.318	0.696**	1.000			
GGT	−0.402	0.190	0.104	−0.451*	0.025	−0.375	0.571**	0.433	1.000		
Triglycerides	0.205	−0.074	0.005	−0.233	0.395	−0.467*	−0.014	−0.188	0.004	1.000	
Cholesterol	0.252	−0.290	0.262	0.119	0.391	−0.112	−0.082	−0.187	−0.522*	0.320	1.000
HDL-cholesterol	0.045	−0.170	0.179	0.279	0.143	0.160	−0.149	0.101	−0.278	−0.448*	0.300

*; **; BMI; V/S; CT-L; CT-S; ALT; AST; GGT; HDL: See legend to Table 1. TG; Chol.: See legend to Table 2.

Table 6 Partial correlation matrix of the listed variables based on the data of 25 females in Table 5

	Age	V/S	CT-L	CT-S	CT-L/CT-S	ALT	AST	GGT	TG	Chol.	HDL-Chol.
Age	1.000										
V/S	0.145	1.000									
CT-L	0.376	0.000	1.000								
CT-S	0.244	0.129	0.239	1.000							
CT-L/CT-S	0.187	−0.127	0.722**	−0.486*	1.000						
ALT	−0.744**	−0.171	−0.577*	0.005	−0.536*	1.000					
AST	−0.663**	−0.162	−0.115	0.211	−0.264	0.616**	1.000				
GGT	−0.364	0.083	−0.438	−0.070	−0.341*	0.526*	0.348	1.000			
Triglycerides	0.257	−0.011	−0.223	0.406	−0.468	−0.065	−0.225	0.003	1.000		
Cholesterol	0.419	0.259	0.325	0.440	−0.056	−0.240	−0.234	−0.631*	0.268	1.000	
HDL-cholesterol	0.095	0.209	0.329	0.130	0.177	−0.149*	0.218	−0.261	−0.594*	0.127	1.000

*; **; V/S; CT-L; CT-S; ALT; AST; GGT; HDL: See legend to Table 1. TG; Chol.: See legend to Table 2.

Table 7 List of the selected variables in multiple regressinon analysis when ALT was taken as the independent variable

	Variable	Regression coefficient	*t* value
Male			
F value = 14.3***	Ratio of CT-L/CT-S	−17.7	−2.13*
$r^2 = 0.627$	Age	0.36	−2.54*
	BMI	1.84	3.26**
	GGT	0.33	4.22***
Female			
F value = 35.5***	Ratio of CT-L/CT-S	−24.2	−3.5**
$r^2 = 0.725$	Age	−1.0	−6.4***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; CT-L; CT-S; BMI; GGT: See legend to Table 1.

ing the positive correlation observed between the fatty change of the liver and the visceral obesity.

Results of correlation analysis on the female data in Table 1 are shown in Table 5. No significant correlations were found between the variables related to fatty change of the liver (CT-L/CT-S) and V/S. The ratio of CT-L/CT-S showed meaningful negative correlation with ALT and triglycerides. ALT also negatively correlated with CT-L, age and triglycerides. GGT negatively correlated with CT-L and cholesterol. Thus, the fatty change of the liver was reflected in blood biochemistries such as ALT rather than the index of obesity (BMI). The correlation coefficients calculated on the basis of all the available data of variables on 36 females in Table 1 were similar (Table 5). The results of partial correlation analysis of the females (Table 6) did not show significant negative correlation between CT-L/CT-S ratio and the V/S ratio either.

Since ALT is a well established marker of fatty liver, a multiple regression analysis was made on the data given in Tables 2 and 5 by taking ALT as the independent variable (Table 7). Four variables including CT-L/CT-S, age, BMI and GGT were selected. The regression coefficients (*t* value, $P < 0.05$) were −17.7, −0.36, 1.84 and 0.33, respectively. The coefficient of determination (r^2) was calculated to be 0.627 (F value < 0.001) in the males. In the females, two variables including CT-L/CT-S and age were selected, the regression coefficients (*t* value, $P < 0.05$) being −24.2 and −1.0, respectively. The value of (r^2) was calculated to be 0.725 (F value < 0.001) in the females.

The odds ratio in favor of CT-L/CT-S < 1, which represents fatty liver, with V/S > 1, which represents viesceral obesity, was 3.25 (95% confidence interval: 1.02–10.39) in the males and 1.15 (95% confidence interval: 0.0–19.68) in the females, further supporting the association between the fatty liver and visceral obesity.

There were no significant differences in the CT-L/CT-S ratio, V/S, markers of the hepatic function or fat deposition between subjects with a history of alcohol intake and those without. Those who had a habit of daily intake of alcohol, drank 1 to 2 goes (180 ml) of sake or 1 to 2 cans (350 ml) of beer. However, there were significant differences in average age (45.7 ± 11.6 years old, $P < 0.01$), BMI ($25.5 \pm 2.7\,kg/m^2$, $P < 0.05$) and GGT ($37.3 \pm 23.0\,IU/l$, $P < 0.05$) between the groups with and without alcohol intake in both males and females when combined as a common population. However, there was a significant difference in individual age (45.6 ± 12.1,

$P < 0.01$) only among the men NEFA analyzed on 32 males and 26 females showed a positive correlation with AST in both groups.

Discussion

We demonstrated in this study a close association between the fatty liver and the visceral obesity by analyzing the correlation between the variables or indices of fatty liver and the V/S ratio, the latter being a well-documented index of visceral obesity (8, 9). As a measure of fatty liver, lower CT number is generally accepted, although the decrease in CT number of the liver relative to that of the spleen is also routinely used (6). Since there seemed to be common factors affecting the CT number of the liver and the spleen, as revealed by the significant correlation existing between CT-L and CT-S in this study, it would be reasonable to use the CT-L/CT-S ratio as an index of fatty liver by eliminating such factors. In fact, there was a higher negative correlation existing between the CT-L/CT-S ratio and the V/S ratio than that between the CT-L and the V/S ratio, the latter being statistically not significant (Table 2). This would consolidate the idea of using the CT-L/CT-S ratio as an index of fatty liver. The significantly high odds ratio in men also supported this concept.

However, ALT, another clinical marker of fatty liver (1) correlated negatively with both CT-L and the CT-L/CT-S ratio in the female group. Since ALT also correlated negatively with age, it may represent an age-related change in the liver CT number, although the correlation between CT-L and age was not statistically significant probably because of the small number of subjects entered into the analysis.

The significant partial regression coefficient of GGT in men is probably related to their history of alcohol consumption (10), although we did not obtain any evidence that the fatty liver or visceral obesity is related to the alcoholic intake.

As it is evident from the results of this study that BMI is related to both visceral and subcutaneous obesity, BMI is likely to constitute a confounding factor in analysis with the V/S ratio. As a result of partial correlation analysis, BMI was found to have been acting as a negative confounding factor as judged by the increased correlation coefficient between the CT-L/CT-S ratio and the V/S ratio. Another reason why BMI did not show any significant correlation with the obesity-related variables, such as triglyceride and HDL-cholesterol in men and triglyceride, cholesaterol and HDL-cholesterol in women, would be partly accounted for by a particular population with the BMI above 22, which was employed in this study. This was because the aim of this study was to find variables which correlate with the V/S ratio and not with simple obesity.

As for the mechanism of fat deposition in visceral obesity, it would be reasonable to assume that the NEFA released from the visceral adipose tissue will overload the liver as triglyceride precursors through the portal blood flow. Rapid turnover of the fat in visceral adipose tissue under dietery or physically stimulated conditions is well documented (11-13). Although physical exercise will release NEFA from the visceral adipose tissue, it will eventually reduce fat deposition in the liver as the amount of viceral fat is exhausted. Restriction of total energy intake in addition to the physical exercise is not exceptional for the treatment of fatty liver as well as obesity.

The lack of association between the V/S ratio and atherogenic indices, such as triglycerides, cholesterol or HDL-cholesterol, would be due to a particular population shifted toward obesity. Nevertheless, the importance of fatty liver as a disease related to atherogenesis should be considered in future studies on the basis of the significant correlation existing between fatty liver and visceral obesity.

In conclusion, the results of our study indicated that there is a significant association between fatty change in the liver and visceral obesity and that the CT-L/CT-S ratio can be considered as a better marker of fatty liver (fatty change) than CT-L.

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